Am. J. Hum. Genet. 41:1083–1103, 1987

Genetic Risk for Recombinant 8 Syndrome and the Transmission Rate of Balanced Inversion 8 in the Hispanic Population of the Southwestern United States

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SUMMARY

A rec(8) dup(q) syndrome, secondary to a pericentric inversion—inv(8)(p23q22)—has been identified in 26 probands from Hispanic kindreds in the southwestern United States. The clinical phenotype of the Hispanic rec(8) syndrome includes a dysmorphic facies, cardiovascular and urinary-tract malformations, and mental retardation. Segregation analysis utilizing pedigree and cytogenetic data from 31 kindreds including five additional kindreds from additional sources has provided computation of genetic risks for counseling. An inv(8) carrier parent has a 6.2% risk of having a rec(8) child. The transmission rate of the inv(8) was significantly higher for inv(8) carrier mothers (59%) than for carrier fathers (42%). The combined transmission rate for both sexes was 53%. Risk for spontaneous abortion or stillbirth (11.3%) was not higher than the general population frequency of 13%–15%. It is significant that all kindreds identified to date are of Hispanic background with ancestors traced to the southern Colorado/northern New Mexico region. By means of extended pedigree information, three independently ascertained kindreds have been linked through common ancestry 4 generations in ascendance. The Hispanic background, geographic localization, and common ancestry in three kindreds suggest a single founder of the Hispanic inv(8) in the Southwest.

Received January 15, 1987.

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INTRODUCTION

Pericentric inversions (PIs) have been reported for almost all human chromosomes. The most commonly reported inversion, inv(9)qh, is estimated to occur in ~1%–1.5% of normal individuals (de la Chapelle et al. 1974; Madan and Bobrow 1974; Boué et al. 1975; Zabel et al. 1977). For other PIs, excluding inv(9) cases, the incidence, in surveys of newborns, has varied from 0.01% to 0.03% (Nielsen and Sillesen 1975; Evans 1977; Hook and Hamerton 1977; Jacobs 1977, 1981; Walzer and Gerald 1977), and, in prenatal diagnosis surveys, from 0.12% to 0.22% (Crandall et al. 1980; Boué et al. 1982; Verjeslev and Friedrich 1984).

Although certain PIs, e.g., inv(9)(p11q12), can now be considered normal variants, other PIs carry a significant reproductive risk (Sutherland et al. 1976; Trunca and Opitz 1977; Dutrillaux et al. 1980; Daniel 1981). The present paper will focus on risk factors. Recombinant aneusomies have been reported for a number of autosomes, including chromosomes 3–11, 13–15, 17, 18, 20, 21, and 22, as well as for the X and Y chromosomes (Dutrillaux et al. 1980; Kaiser 1984; Mosher and Sanger 1985; Greenberg et al. 1986). It is estimated that approximately one-third of the familial PIs produce documented recombinant offspring (Dutrillaux et al. 1980). The risk for a balanced-inversion heterozygote to have a recombinant offspring is dependent on (1) the size of the distal segments from the breakpoints of the inverted chromosome, (2) the distribution of chiasmata along the chromosome—and thus the probability of a meiotic crossover occurring within the inversion, and (3) the probability that at least one of the two recombinant chromosomes would produce a viable offspring (van der Linden et al. 1975; Trunca and Opitz 1977; Winsor et al. 1978; Daniel 1981; Kaiser 1984). The frequency of crossovers is related to the regional location and to the type and length of chromosome material included in the inversion. The greater the amount of chromosome material within the inverted segment, the smaller the relative sizes of distal segments that would be duplicated or deleted, thus increasing the probability of a viable recombinant offspring (Trunca and Opitz 1977; Winsor et al. 1978; Dutrillaux et al. 1980; Mattei et al. 1980; Daniel 1981; Kaiser 1984).

Estimating risks of recombinant offspring for familial PIs poses a difficult and increasingly frequent problem for genetics counselors. If the parental inversion is ascertained through a recombinant offspring, the recurrence risk has been estimated to be as high as 10% (Sutherland et al. 1976). The risk of a recombinant offspring in a family ascertained through a balanced-inversion carrier with no previously documented recombinants has been suggested to be 1% (Sutherland et al. 1976). Reports on specific cases of familial inv(18), resulting in rec(18) offspring, have given empiric risks of 10% in three families (Vigi et al. 1977) and of 5% in five families (Teyssier and Bajolle 1980). An unusually high empiric risk of 40% for either one of the possible two recombinants in one extended family with inv(13)(p11q22) has been reported (Williamson et al. 1980). Most of the reports, however, have been based on a limited sample size for each specific chromosome inversion.

Relatively little information concerning genetic risk has been available for chromosome 8 inversions. Four different classes of inv(8) have been reported (table 1). Of these, only the inv(8)(p23q22), identified in the Hispanic population (fig. 1), has been reported to result in recombinant offspring (Fujimoto et al. 1975, 1978; Peakman et al. 1977; Moedjono and Sparkes 1980; Grix et al. 1981; Sujansky et al. 1981). The Hispanic inv(8) encompasses 74% of chromosome 8. The inversion identified in a Canadian family (Aveling et al. 1977) is defined by the same breakpoints; whether it is indeed identical to that observed in the Hispanic families needs to be determined. The Canadian family exhibits a high incidence of miscarriage and no documented recombinant offspring (P. W. Allderdice, personal communication). An inv(8) with breakpoints apparently identical to those of the U.S. Hispanic inv(8) was documented in an Argentinian mother with a rec(8) dup(q) child (Coco et al. 1979; Lovell et al. 1982). An extensive pedigree for this South-American family has not been reported.

The Hispanic inv(8) was first reported by Fujimoto et al. (1975), who identified an inv(8)(p23q22) in a Hispanic woman who had given birth to a child with rec(8) dup(q). Subsequently the rec(8) syndrome has been described in additional Hispanic kindreds from several Western states (Peakman et al. 1977; Fujimoto et al. 1978; Moedjono and Sparkes 1980; Grix et al. 1981; Sujansky et al. 1981). The rec(8) has a duplication of the distal segment of the long arm (8q22-qter) and a deficiency of a small portion of the distal end of the short arm (8p23-pter) (fig. 1). High-resolution analysis of chromosomes of Colorado kindreds has indicated more refined breakpoints of the inversion at 8p23.1 and 8q22.1. The distal segments at the breakpoints, 8p23.1 and 8q22.1, comprise only 0.44% and 1.59%, respectively, of the haploid autosome length (HAL) of inv(8) (Daniel 1985). Apparently this inv(8) yields a small enough monosomy and trisomy of these segments in the recombinant chromosome to allow viability. The clinical phenotype associated with the Hispanic rec(8) has been relatively consistent for all documented cases (fig. 2), including a characteristic dysmorphic facies, cardiovascular and urinary-tract anomalies, cryptorchidism in males, and moderate to severe mental retardation (Sujansky et al. 1981, 1986; Clericuzio and Aase 1984; Williams et al. 1984).

The majority of cases have been identified in Southern Colorado and Northern New Mexico. Ancestral lines of cases, who were ascertained in California and Utah (LL001, LA001, LA002, and SL001 in the Appendix), also have been traced to this region of the Southwest (fig. 3). In those cases in which parental chromosomes have been studied, a pericentric inv(8) identical to that described by Fujimoto et al. (1975, 1978) has been found. The rec(8) female child from the Argentinian family presented similar clinical defects (Lovell et al. 1982).

Two of the three reported classes of inv(8) appear to have a very low risk for recombinant offspring (table 1). The lack of reported recombinant offspring for inv(8)(p23q11) is probably related to the rather large HAL percentage in the potentially imbalanced distal segments. Although the more rare inv(8)(p11q24) has an HAL percentage in the distal segments comparable to that of the Hispanic inv(8), it has been associated with multiple abortions in one reported family. The Hispanic inv(8) carries a more significant reproductive risk. To

TABLE 1

REPORTS OF PI OF CHROMOSOME 8

Reference	Inversion	Ascertainment	Documented Recombinant Offspring
Herva and de la Chapelle 1976	inv(8)(p11q24)	History of repeated miscarriage	None
Jacobs et al. 1967, 1974	inv(8)(p23q11)	Secondary amenorrhea	None
		Congenital anomalies	None
		Survey of prisoners	None
		Congenital anomalies	None
Ferguson-Smith 1967	inv(8)(p23q11)[a]	Congenital anomalies	None
Bui et al. 1982	inv(8)(p23.1q12.1)	Prenatal diagnosis	None
Breg et al. 1972	inv(8)(p23q22)	Mental retardation	None
Aveling et al. 1977	inv(8)(p23q22)	History of repeated miscarriage	None
Fujimoto et al. 1975, 1978	inv(8)(p23q22)	Recombinant offspring	rec(8) dup(q)
Peakman et al. 1977	inv(8)(p23q22)	Recombinant offspring	rec(8) dup(q)
Moedjono and Sparkes 1980	inv(8)(p23q22)	Recombinant offspring	rec(8) dup(q)
Sujansky et al. 1981	inv(8)(p23q22)	Recombinant offspring	rec(8) dup(q)
Lovell et al. 1982	inv(8)(p23q22)	Recombinant offspring	rec(8) dup(q)
Kawana et al. 1976	inv(8)(p23q23)	De novo congenital anomalies	None
Grix et al. 1981	inv(8)(p23.2q23.1)	Recombinant offspring	rec(8) dup(q)

[a] Breakpoints described in Herva and de la Chapelle 1976.

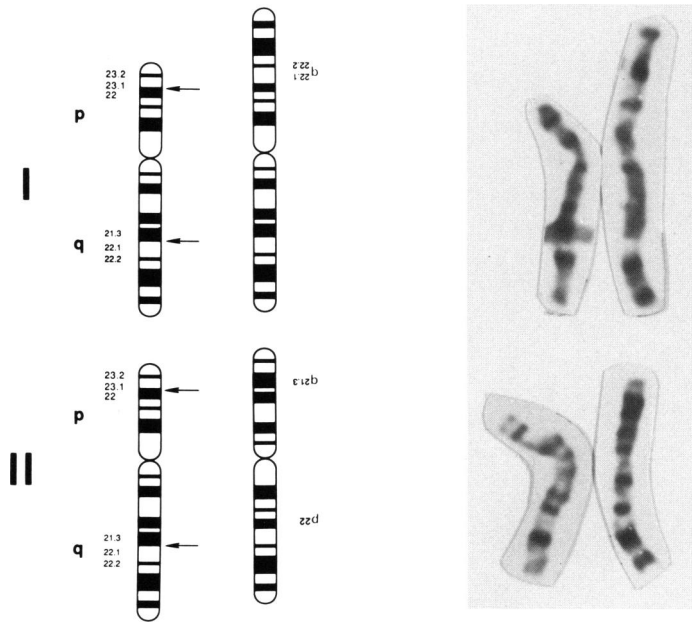


FIG. 1.—Schematic representation and chromosome 8 pairs illustrating recombinant chromosome 8 [rec(8)(p23.1q22.1) dup(q)] (*I*) and pericentric inversion 8 [inv(8)(p23.1q22.1)] (*II*).

obtain reliable risk estimates for genetic counseling of inv(8) carriers, detailed pedigrees from kindreds that had undergone cytogenetic analysis were analyzed.

MATERIAL AND METHODS

The study population included 24 Colorado (C) and New Mexico (NM) kindreds ascertained via a cytogenetically documented rec(8) proband. A summary of the family pedigrees used in the analysis is included in the Appendix. Two additional inv(8) kindreds, C017 and NM010, ascertained through prenatal diagnosis for advanced maternal age, were also included. The fetal karyotypes in these cases were inv(8)(p23q22). Cytogenetic analyses using trypsin G-banding were performed on relatives to identify inv(8) carriers. Medical information and, when available, photographs were requested on all individuals with multiple birth defects and/or congenital heart disease (CHD) who were deceased and not available for cytogenetic analysis. In these circumstances individuals were defined as "presumed rec(8)" if (1) their clinical reports were consistent with the rec(8) phenotype and (2) the parent was a documented inv(8) carrier. A sibship for which the sex of the carrier parent was unknown (i.e., five sibships with deceased parents, grandparental to the rec(8) proband) was included in the analysis to estimate average risks if the parent was an obligate carrier. A parent was defined as an obligate carrier if at least two inv(8) carriers were documented among the offspring. Also, five additional kindreds

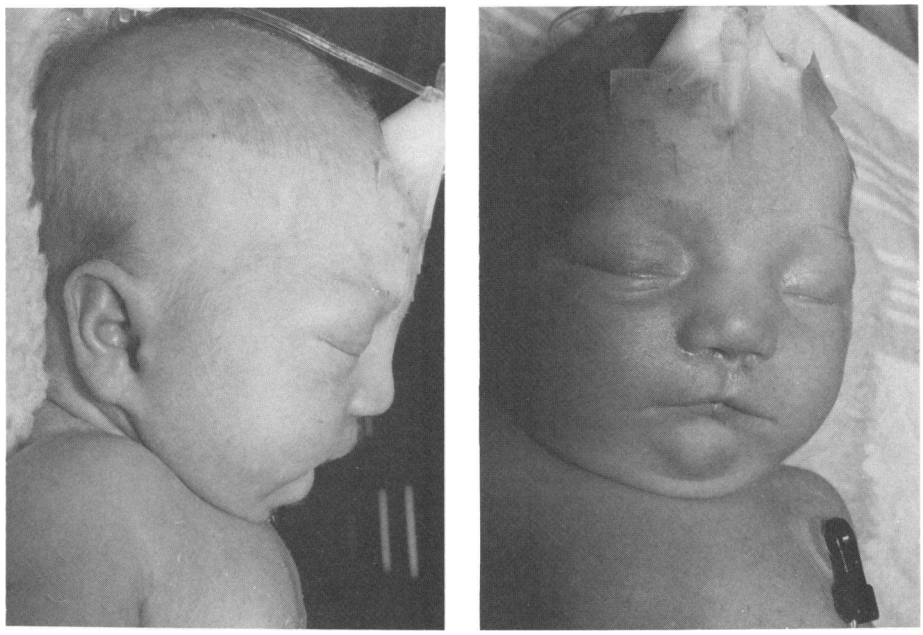


FIG. 2.—Patient with Hispanic rec(8) syndrome. Note long philtrum, hypertelorism, and depressed nasal bridge.

ascertained through a rec(8) proband (Appendix)—two of these five being reported in the literature (LA001 [Fujimoto et al. 1975, 1978] and LA003 [Moedjono and Sparkes 1980] and three being noted in personal communication (LL001 [C. Sandlin], LA002 [A. Fujimoto and W. Herbert], and SL001 [E. Stierman])—were included in the analysis.

In the 31 kindreds (Appendix), 393 individuals (representing 119 total sibships) have been studied cytogenetically, and 36 rec(8) offspring and 211 inv(8) carriers have been identified. Detailed pedigree and cytogenetic data, spanning as many as 4 generations, have been collected from these kindreds; seven provided 1 generation of sibships, 14 provided 2 generations of sibships, and 10 provided 3 generations of sibships informative for risk analysis. Sufficient pedigree information was obtained from the kindreds to estimate the probability of a balanced inv(8) carrier parent having (1) a rec(8) offspring, (2) an inv(8) carrier offspring, and (3) a spontaneous abortion (SAB) or stillbirth. Risks for inv(8) mothers and inv(8) fathers were determined separately. Segregation analysis, using maximum-likelihood method (Morton 1959), was used to estimate these risk values on the basis of the informative sibships.

For segregation analysis of the rec(8) chromosome, 108 sibships (including 48 paternal, 59 maternal, and one sex-unknown carrier) were analyzed. Sibships were classified according to ascertainment type on the basis of either (1) a rec(8) proband (single selection), (2) the proband's inv(8) carrier parent or grandparent (the direct forebear was excluded from the ascendant sibship to

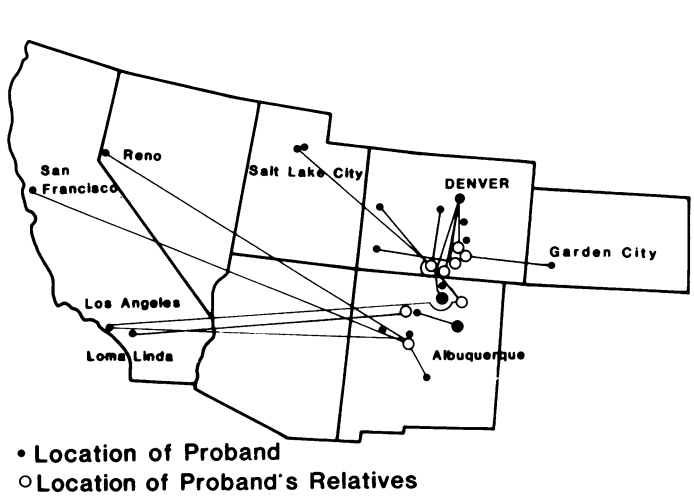


FIG. 3.—Geographic localization of relatives of documented rec(8) probands

reach complete selection), or (3) an inv(8) carrier parent (e.g., sibship of proband's cousin, complete selection).

For segregation analysis of the balanced inv(8) chromosome, 104 sibships (43 paternal, 56 maternal, and five sex-unknown carriers) were analyzed. Sibships were classified according to ascertainment type on the basis of either (1) a rec(8) proband (proband's sibship, excluded proband for complete selection), (2) an inv(8) parent or grandparent of the proband (direct-forebear sibship, single selection), or (3) an inv(8) carrier parent (complete selection). In the analysis of fetal wastage, no kindred was ascertained on the basis of multiple miscarriages. Risk for SAB or stillbirth was calculated for 111 sibships (48 paternal, 61 maternal, and two sex-unknown carriers). Sibships were classified according to ascertainment on the basis of either (1) a rec(8) proband or a parent of the proband (single selection) or (2) an inv(8) carrier parent (complete selection). Sufficiently detailed and reliable reports of miscarriages and stillbirths from noncarrier parents were not obtained during the collection of family histories; thus, comparison of the frequencies of SABs and stillbirths among carrier and noncarrier parents within the same kindreds was not possible.

RESULTS

The numbers of (1) male and female recombinant offspring, (2) male and female balanced-inversion carrier offspring, and (3) SABs/stillbirths from inv(8) mothers and from inv(8) fathers in the 31 kindreds are shown in table 2. The sex ratio for rec(8) offspring and inv(8) offspring in sibships from either a carrier mother or carrier father was consistent with a 1:1 ratio. χ^2 2 × 2 Tests (χ^2_1) for association indicated no differences in any offspring frequency category between carrier parents. Although more inv(8) offspring data have been

TABLE 2

NUMBER OF INDIVIDUALS IN THE DIFFERENT RISK CATEGORIES FOR SIBSHIPS (31 Kindreds) CLASSIFIED ACCORDING TO THE SEX OF THE CARRIER PARENT

STATUS AND GENDER	CARRIER PARENT	
	Male (N = 50)	Female (N = 68)
Rec (8) probands:		
Male	11	4
Female	7	7
Total	18	11
All rec (8) offspring:		
Male	15	13
Female	11	15
Total	26	28
Inv(8) offspring:		
Male	28	62
Female	29	68
Total	57	130
Documented normals:		
Male	28	34
Female	33	32
Total	61	66
Total offspring:		
Male	84	151
Female	78	131
Total	162	282
SABs and stillbirths	17	23
Mean ± SEM average sibship size	3.3 ± 0.3	4.1 ± 0.4

obtained from carrier mothers than from carrier fathers, the relative numbers of all male and female offspring are essentially equivalent for each carrier sex (table 2). In sibships from carrier fathers and in those from carrier mothers, the numbers of documented SABs or stillbirths were similar. The number of stillbirths reported from all kindred histories was low; two were from inv(8) fathers, four from inv(8) mothers, and one from an obligate carrier, sex unknown. The average sibship sizes for the kindreds were 3.2 from carrier fathers and 4.1 from carrier mothers (table 2).

The genetic risks of (1) a rec(8) offspring, (2) an inv(8) carrier offspring, and (3) an SAB or stillbirth from a carrier parent are listed in table 3. Segregation analysis indicated that frequencies of rec(8) offspring from male (5.9%) and female (6.6%) inv(8) parents are essentially the same ($\chi^2_1 = 0.07$ for heterogeneity between sexes). There was no heterogeneity between types of ascertainments or types of sibships. An average value of 6.2% can be given as the risk of an inv(8) carrier parent having a rec(8) child.

The transmission rate of the balanced inv(8) chromosome is 42% and 59% for a paternal carrier and a maternal carrier, respectively. Thus, segregation of the inv(8) was found to be significantly higher in offspring from a carrier mother than in offspring from a carrier father (heterogeneity χ^2_1 between sexes = 7.44;

TABLE 3

RISK OF REC(8) dup(q) OFFSPRING AND SAB OR STILLBIRTH, AND TRANSMISSION RATE OF BALANCED-INV(8) OFFSPRING FROM INV(8)-CARRIER PARENT

Segregation	Fathers	Mothers	Pooled Sexes
Rec(8)	.059 ± .020	.066 ± .017	.062 ± .013
Inv(8)	.422 ± .049	.593 ± .038	.533 ± .029
SAB or stillbirth	.125 ± .027	.086 ± .020	.113 ± .016

$P < .01$). Analysis of the pooled data from both sexes gives an average 53% transmission rate. This average value is not significantly higher ($\chi^2_1 = 1.12$) than the 50% expected segregation frequency. However, the segregation frequency of inv(8) offspring from carrier mothers is significantly greater than 50% ($\chi^2_1 = 5.56$; $P < .01$); the frequency from carrier fathers is not ($\chi^2_1 = 2.51$). There was no heterogeneity between types of ascertainments or types of sibships.

The risk of SAB or stillbirth was 12.5% for carrier males and 8.6% for carrier females ($\chi^2_1 = 1.39$ for heterogeneity between sexes; not significant). The average risk was 11.3%. These risk figures do not differ significantly from the 13%–15% approximate risk for SABs reported for the general population (Boué and Boué 1973; Kline et al. 1977; Wilcox et al. 1981). There was no heterogeneity between types of ascertainment.

DISCUSSION

Carriers of the pericentric inv(8) may produce two abnormal recombinant chromosomes, but only one recombinant—rec(8) dup(q), inv(8)(p23q22)—has been identified in these kindreds. The second recombinant chromosome rec(8) dup(p) would have a duplication of the terminal material of the short arm (8p23.1-pter) and a large deletion of material from the distal segment of the long arm (8q22.1-qter). This latter type has never been documented, and it might well be lethal owing to the consequent larger partial monosomy and smaller partial trisomy. To determine whether the few stillbirths and SABs reported in the rec(8) kindreds represent dup(p) requires further study. This absence of the dup(p) recombinant is in agreement with the general observation that viable chromosome recombinants include structural rearrangements with larger proportions of trisomic segments and smaller proportions of monosomic segments (Daniel 1981; Kaiser 1984). Since three other inversions—inv(5)(p13q35) (Warter et al. 1973), inv(18)(p11q21) (Vianna-Morgante et al. 1976), and inv(13)(p11q22) (Williamson et al. 1980)—have resulted in progeny with both possible recombinants, it is important eventually to determine whether the Hispanic inv(8) ever results in the birth of a child with rec(8) dup(p).

Although homozygous carriers of a pericentric inv(9) and inv(3) have been reported (de la Chapelle et al. 1974; McKenzie and Lubs 1975; Vine et al. 1976; Fogle and McKenzie 1980), no person homozygous for inv(8)(p23q22) has been found to date. In view of the tendency of rec(8) families to originate predomi-

nantly from small, rather isolated communities located in northern New Mexico, a certain degree of inbreeding and homozygosity for inv(8) might well be found. It is important to identify such individuals for the following two reasons: (1) all of their children would be inv(8) carriers and, therefore, at risk for having rec(8) offspring; and (2) although balanced-inversion heterozygotes appear to be phenotypically normal, it is unknown whether the homozygous inv(8) would result in any clinically recognizable phenotypic anomalies.

Previously, the general risk for a PI carrier to have a recombinant offspring has been cited as 10%. On the basis of very limited family data, it has been suggested further that this risk could be lower for carrier fathers than for carrier mothers (Sutherland et al. 1976). The 10% risk value was determined on the basis of several different familial PIs. Our analysis indicates that the average risk of inheriting the recombinant chromosome 8 is <10% (i.e., 6.2%). Moreover, the higher risk of rec(8) offspring from inv(8) carrier mothers than from carrier fathers was not found. The 6.2% risk is similar to that found in the European Prenatal Diagnosis Collaborative Study of PI (Boué and Gallano 1984), which reported an average of 5.9% unbalanced offspring from a balanced-inversion carrier (4% from paternal carriers and 7.5% from maternal carriers in 118 families).

It is noteworthy that none of the Hispanic inv(8) kindreds have been ascertained through a reported occurrence of multiple abortion. The 11.3% risk for miscarriage or stillbirth in inv(8) carrier parents does not exceed the 13%–15% SAB frequency for the general population (Boué and Boué 1973; Kline et al. 1977; Wilcox et al. 1981); nor does it greatly exceed the 9.1% SAB risk computed for PI carriers not ascertained through SABs (Kaiser 1984). The fact that the rec(8) dup(p) has never been documented and the absence of a reported high frequency of miscarriages suggest the possibility of very early lethality of the dup(p) recombinant.

It is of interest that the transmission rate of inv(8) is significantly higher than the expected 50% in carrier mothers but not greater than the expected rate in carrier fathers. Hypotheses that might explain this segregation distortion, by relating genetic mechanisms to differential gametic selection between the sexes, await further study. A few other reports have also found evidence of differential segregation of chromosomal rearrangements between the sexes. In a small sample of 18 inv(12)(p11.2q13.1) and inv(12)(p12.3q13.1) families from one large kindred, increased segregation from carrier mothers was indicated ($P = .026$ by Fisher's exact test; Poulsen et al. 1981). A higher frequency of inv(4)(p15.2q11) carriers from carrier mothers than from carrier fathers has also been observed in pedigrees from two unrelated families ($P = .005$ by Fisher's exact test; Baccichetti et al. 1982). It is also of interest that in three kindreds with a reciprocal translocation involving chromosome 8—viz., t(1;8)(q41;q23.1)—an excess of carrier offspring from maternal carriers was suggested ($P = .113$ by Fisher's exact test; Vauhkonen et al. 1985). In contrast, a recent report of two inv(12)(p11.2q13) families noted an excess of balanced inv offspring from both maternal and paternal carriers (Voiculescu et al. 1986).

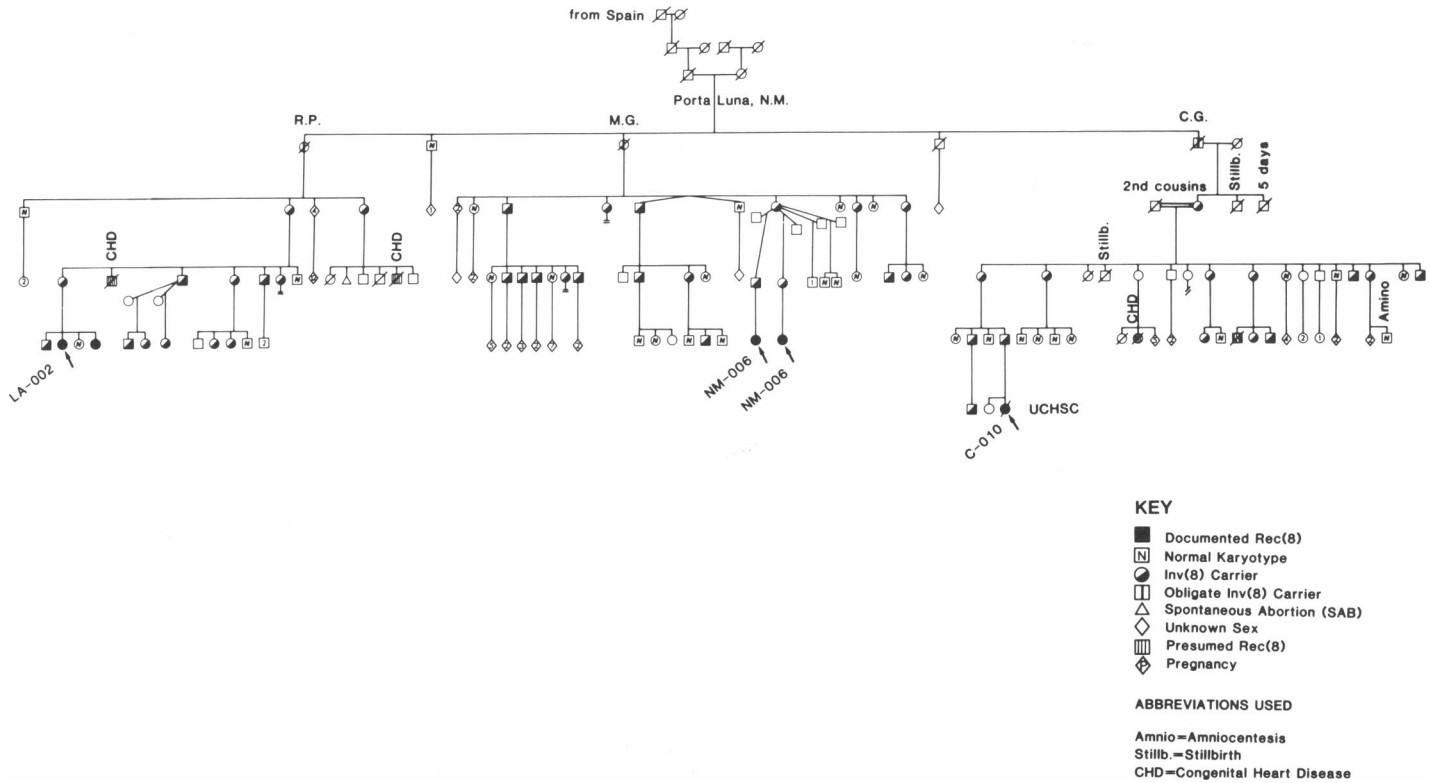


FIG. 4.—Three inv(8) kindreds from Los Angeles, California, Colorado, and New Mexico linked through common ancestry

Recently, a segregation analysis of balanced PIs from 216 different inversion pedigrees found no evidence of segregation distortion of PIs in offspring of either carrier parent (Sherman et al. 1986). Furthermore, a reanalysis by Sherman et al. (1986) of data from the European Prenatal Diagnosis Collaborative Study (Boué and Gallano 1984), which had originally suggested an excess of balanced-inversion offspring from carrier fathers, failed to demonstrate any sex difference. In addition, an observed 50% segregation frequency from balanced carrier parents has been reported for specific inversions of chromosomes 9, 10, and 13 (de la Chapelle et al. 1974; Habedank 1982). These findings contrast with the present results of a >50% segregation of inv(8) offspring from carrier mothers. Segregation patterns will vary among distinct inversions. Therefore, combining data of various PIs may in fact obscure subtle differences among inversions (Stene 1986). In the present study pedigree data from the rec(8) kindreds have offered the unique opportunity to analyze the segregation pattern of a single specific inversion.

The recognition of a chromosomal abnormality in these reported cases—an abnormality associated with CHD—was essential for appropriate genetic counseling (Sujansky et al. 1981). Documentation of a familial inv(8) altered the genetic counseling, since the risk of having a rec(8) child with multiple anomalies and mental retardation (3.6%–8.8% risk; 95% confidence interval of the average 6.2% risk) is greater than the risk of having a child with isolated CHD of multifactorial etiology (~3% risk; Nora and Nora 1978, pp. 156–157). Most important with regard to the genetic etiology of CHD in the rec(8) child is that prenatal diagnosis for the recombinant chromosome can be offered as an available option to the documented inv(8) carrier parent.

It is significant that the inv(8) kindreds identified, including the original family described by Fujimoto et al. (1975), are of Hispanic background. Recently, a rec(8) family of North-American-Indian ancestry from the New Mexico Isleta Pueblo has been ascertained. Whether a Spanish ancestor also exists for this family is not known. Through analysis of detailed family histories we have established that three kindreds—C010, NM006, and LA002—each independently ascertained through a rec(8) proband, are linked through common ancestry (fig. 4). Four generations in ascendance, the sibship, in corroborating common ancestry for this extended pedigree, was traced to a village in Northeastern New Mexico, circa late 1800s (fig. 2).

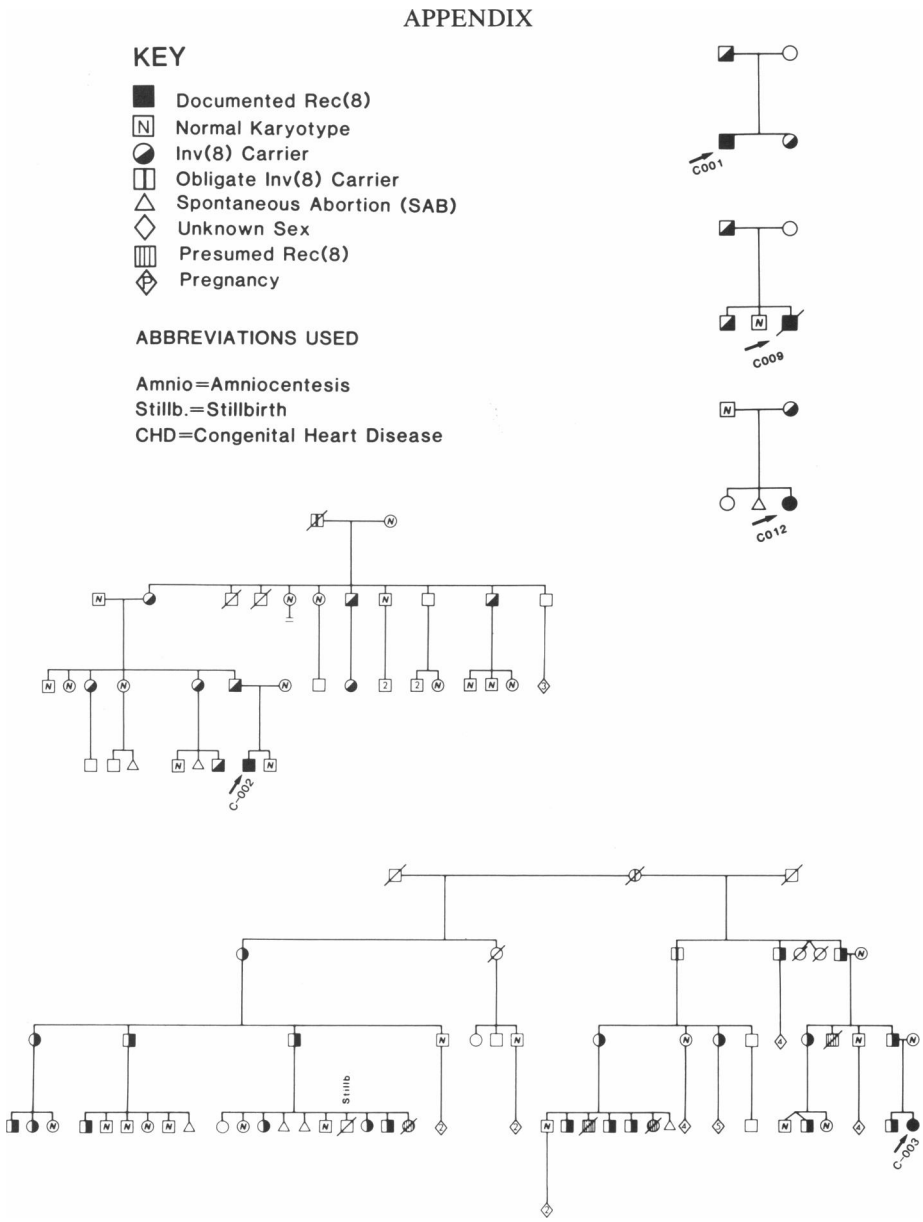
The shared ethnic background and geographical localization, as well as the common ancestry identified for the three kindreds, suggest a common origin (founder effect) of the Hispanic inv(8). Ethnohistorical data regarding the Spanish settlement of the Southwest, specifically of Colorado and New Mexico, is compatible with a possible Spanish "founder." Thus, it appears that the rec(8) dup(q) syndrome was probably ≥1.5 centuries old before the new banding techniques in the 1970s made possible cytogenetic discovery of the disorder.

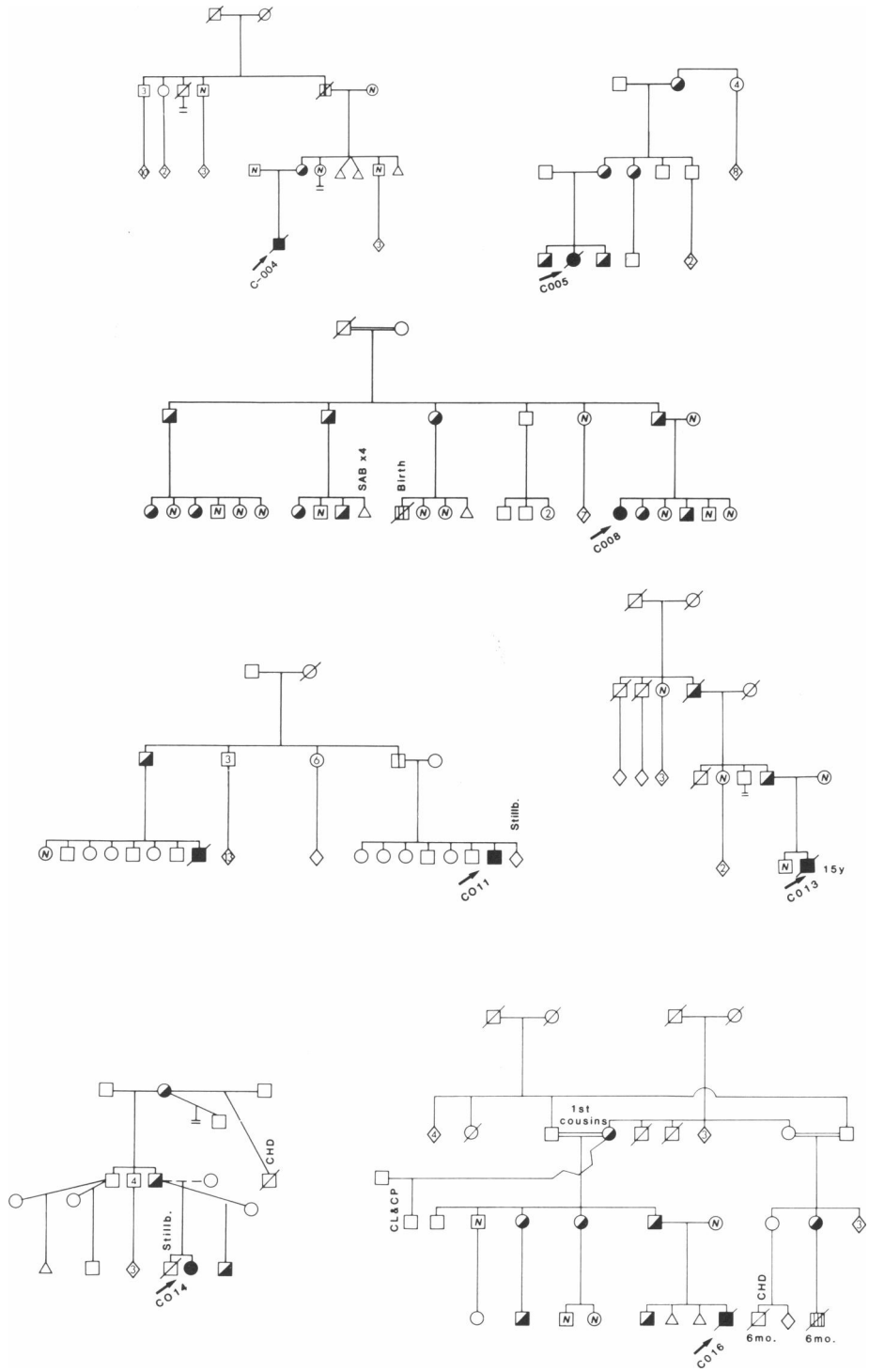
ACKNOWLEDGMENTS

We would like to extend our appreciation to Dr. Connie Sandlin, Dr. A. Fujimoto, William Herbert, and Elizabeth Stierman for providing us with pedigrees of their inv(8)

kindreds. Thanks are also due to Barbara Pettersen, Carol Avery, and Susan Brenman (Genetics Unit, University of Colorado Health Sciences Center) for their assistance in collecting family data, to Dr. Brian Ward and Kathy Taylor (Cytogenetics Laboratory, University of Colorado Health Sciences Center) for cytogenetic analysis of rec(8) families, and to our graphic artist, Nancy Glasgow (The Children's Hospital), for her painstaking artwork representing the pedigrees. Particular thanks is extended to Drs. Newton Morton and Stephanie Sherman for their critical review of the manuscript. This study is supported by National Institutes of Health grants HD 17355 and RR-69, General Clinical Research Centers Program, Division of Research Resources.

APPENDIX

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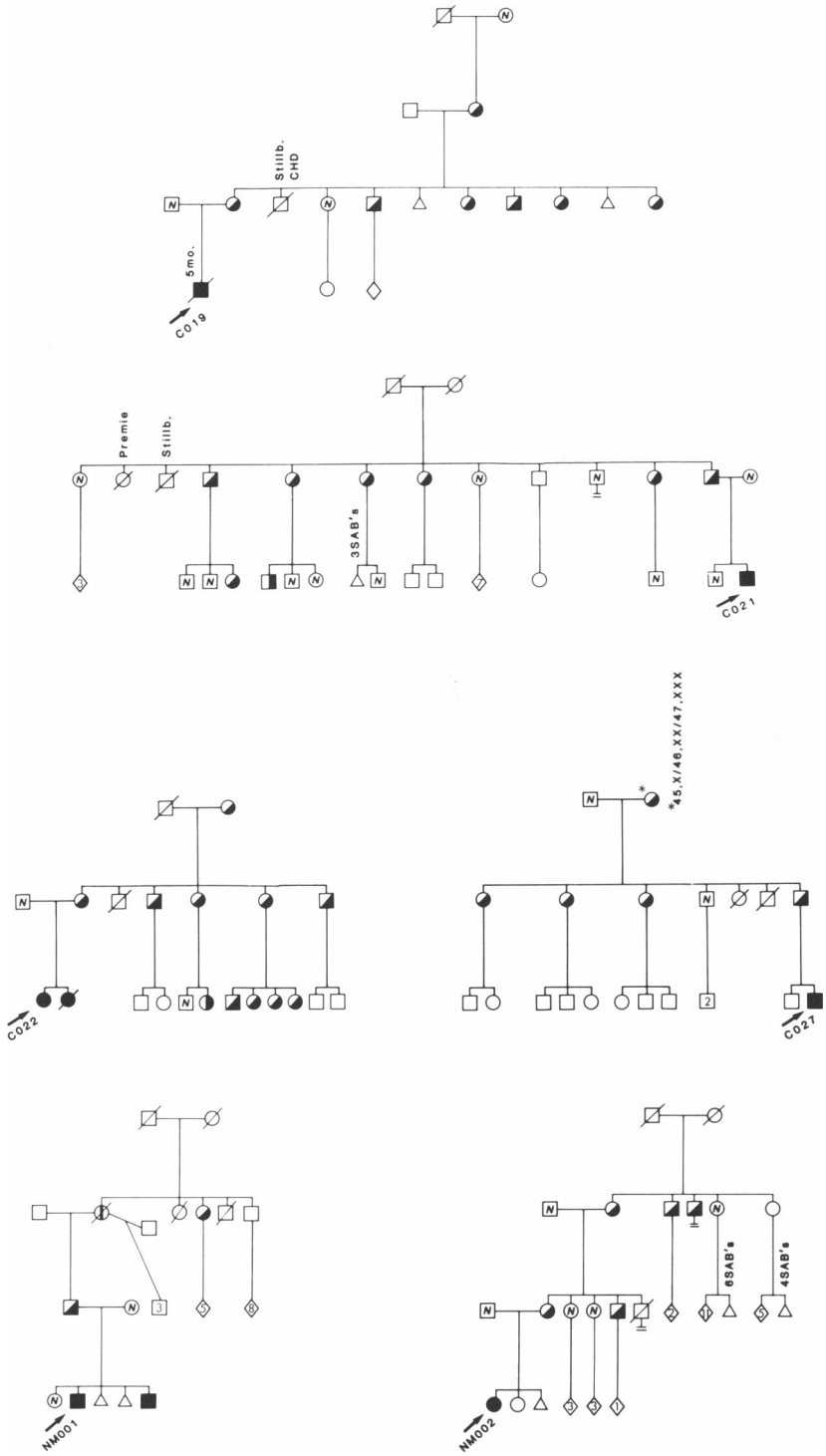
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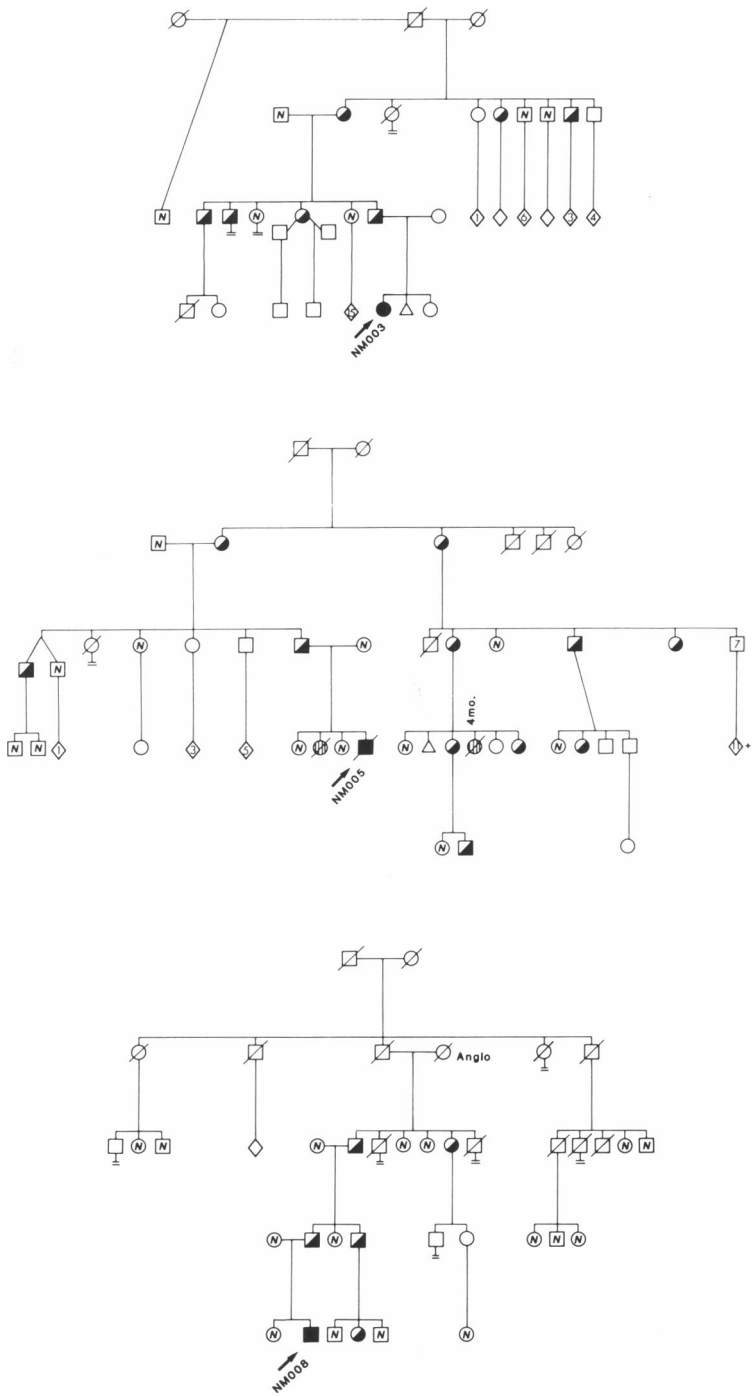
NM001
NM002


NM003
4 mo.
NM005
Anglo
NM008

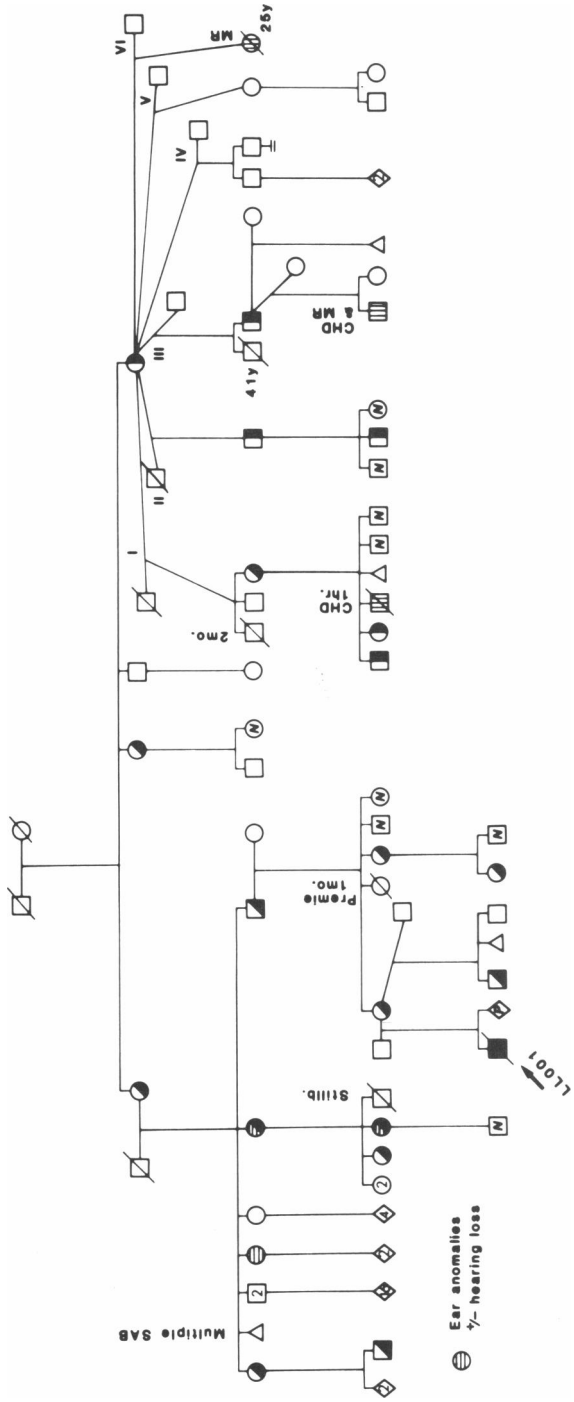

VI
MR
26y
V
IV
CHD & MR
41y
III
II
I
2mo.
CHD 1hr.
Premie 1mo.
LL001
Stillb.
Multiple SAB
Ear anomalies +/- hearing loss

TABLE A1

SUMMARY OF FAMILY DATA OF INV(8) KINDREDS FROM COLORADO AND NEW MEXICO, AND ADDITIONAL KINDREDS FROM SALT LAKE CITY, LOS ANGELES, AND LOMA LINDA, CA

PEDIGREE CODE (No. of Generations)	NO. OF SIBSHIPS STUDIED	NO. OF RECOMBINANT OFFSPRING		NO. OF INVERSION CARRIERS		NO. OF DOCUMENTED NORMALS
		Documented	Presumed	Documented	Obligate	
C001 (1)	1	1	0	2	0	0
C002 (3)	6	1	0	8	1	13
C003 (3)	10	1	4	21	2	14
C004 (2)	2	1	0	1	1	4
C005 (2)	2	1	0	5	0	0
C008 (2)	5	1	1	10	1	12
C009 (2)	2	1	0	3	0	4
C010 (3)	9	1	3	17	1	12
C011 (2)	2	2	0	2	1	3
C012 (1)	1	1	0	1	0	0
C013 (2)	2	1	0	2	0	3
C014 (2)	1	1	0	3	0	0
C016 (2)	5	1	1	9	0	3
C017 (1)	1	0	0	2	0	0
C019 (2)	2	1	0	7	0	1
C021 (2)	7	1	0	9	1	11
C022 (2)	5	2	0	12	0	2
C027 (2)	3	1	0	6	0	3
NM001 (1)	1	2	0	1	0	1
NM002 (3)	3	1	0	5	1	3
NM003 (3)	3	1	0	7	1	4
NM005 (3)	7	1	2	11	0	10
NM006 (3)	10	2	0	18	1	15
NM008 (3)	4	1	0	5	1	7
NM010 (1)	1	1	0	2	0	1
NM011 (1)	1	1	0	1	0	0
LL001 (3)	12	1	3	19	0	9
SL001 (1)	1	1	1	2	0	1
LA001 (2)	3	2	0	5	1	5
LA002 (3)	5	2	2	13	1	4
LA003 (2)	2	1	0	2	0	1
Total (31 kindreds)	119	36	17	211	14	146

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